Diagnostic Value of Thyrotropin-Releasing-Hormone Stimulation in Patients With Pituitary Tumor

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Plasma prolactin response to thyrotropin-releasing-hormone (TRH) stimulation was diminished in 30 patients with prolactinomas and 9 patients with acromegaly who had normal serum prolactin levels. There was no overlap of prolactin responses when compared with 32 control patients. Responses of ten patients with adrenocorticotropin (ACTH)-secreting pituitary tumors were similar to those of controls. Plasma growth hormone concentrations after TRH stimulation changed significantly in 28% of normal control and 20%, 25% and 50% of patients with prolactin-, growth hormone- and ACTH-secreting pituitary tumors, respectively. Our data suggest that the blunted TRH-induced rise in plasma prolactin levels in patients with prolactinomas and those with acromegaly may be related to humoral factor(s) affecting TRH receptor or postreceptor function. Growth hormone responses to TRH are nonspecific and should not be considered a marker for active acromegaly.

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The exact mechanism(s) responsible for the blunted plasma prolactin responses to thyrotropin-releasing-hormone (TRH) stimulation in patients with prolactinomas is unknown. TRH receptors have been found on human prolactinoma cells.[1] In vitro responses of these cells to TRH administration have been variable.[2,3] In most patients with hyperprolactinemia not caused by a pituitary tumor, there is a normal prolactin secretory response to TRH,[4-8] suggesting that ultrashort-loop feedback of prolactin on lactotrope activity is not responsible for the decreased response in prolactinoma patients.

We wondered if the presence of any hypersecreting pituitary tumor might blunt responses to TRH. A tumor mass might impair the local blood supply and thus the delivery of TRH to prolactin-secreting cells, accounting for inadequate responses. Patients with prolactinomas were compared with patients with adrenocorticotropin (ACTH)- and growth hormone-secreting tumors. We found the responses of patients with acromegaly were similar to those of patients with prolactinomas, and patients with ACTH-secreting tumors had responses similar to those of controls. Our studies suggest humoral and not mass lesion effects may explain blunted responses and that growth hormone- and prolactin-secreting tumors are capable of inhibiting prolactin responses to TRH, possibly by a similar mechanism.

Patients and Methods

Controls

Six men and 26 women were studied initially because abnormal pituitary function was questioned clinically. Typical problems included mild obesity (possible Cushing's disease), coarse facial features (possible acromegaly) and possibly a partially eroded sella (verified later as normal by computed tomographic [CT] scan). All findings later proved to be normal except in two patients with primary hypothyroidism and one with drug-induced (thioridazine hydrochloride [Mellaril]) hyperprolactinemia. The two patients with hypothyroidism had pituitary enlargement and hyperprolactinemia: pituitary size and prolactin concentrations reverted to normal with thyroxine therapy.

Prolactinoma

In all, 23 women and 7 men had prolactinomas verified by a surgical procedure. All patients had elevated basal plasma prolactin concentrations. Plasma growth hormone concentrations were normal and suppressed with glucose. All were studied during the preoperative period.

Acromegaly

Four men and five women had acromegaly associated with elevated growth hormone concentrations not suppressible by glucose. None had hyperprolactinemia. All were studied preoperatively.

Cushing's Disease

Ten patients with ACTH-secreting pituitary tumors had detectable levels of plasma ACTH. The diagnosis was established by standard dexamethasone suppression and metyrapone stimulation tests. Plasma growth hormone concentrations were suppressed by glucose in all patients to undetectable levels. All tumors were verified by a pituitary operation. All patients except one were cured by surgical therapy.

All patients were admitted to the Clinical Research Center of the University of Oregon Health Sciences Center. Testing was done between 8 AM and 9 AM in the fasting basal state. After informed consent, 500 μg TRH was given as an intrave-

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ABBREVIATIONS USED IN TEXT
ACTH = adrenocorticotropin
CT = computed tomography
RIA = radioimmunoassay
TRH = thyrotropin-releasing hormone

nous bolus via an indwelling venous catheter. A blood specimen was taken at 0, 20 and 40 minutes through the same catheter and assayed for prolactin and growth hormone by described techniques. Growth hormone was assayed by double-antibody radioimmunoassay (RIA) (BIO-RIA Incorporated, Montreal, Canada). Prolactin was assayed by double-antibody RIA (Diagnostic Products Corporation, Los Angeles).

Results

Prolactin responses to 500 μg TRH are shown in Figure 1. Peak responses were predominantly at 20 minutes, but those occurring at 40 minutes are not identified separately.

Peak plasma prolactin responses are expressed as a percentage increase from basal. TRH-induced changes in plasma prolactin concentrations were significantly different when patients with prolactinomas were compared with either controls ($P < .00001$) or patients with ACTH-secreting tumors ($P < .00001$; Kruskel-Wallis analysis of variance). Patients with growth hormone-secreting tumors had significantly different responses from those of controls ($P < .00001$). There was no significant difference in responses between patients with prolactinoma and those with acromegaly ($P < .5$). Responses expressed in nanograms per milliliter are shown in Figure 2 for all patients studied.

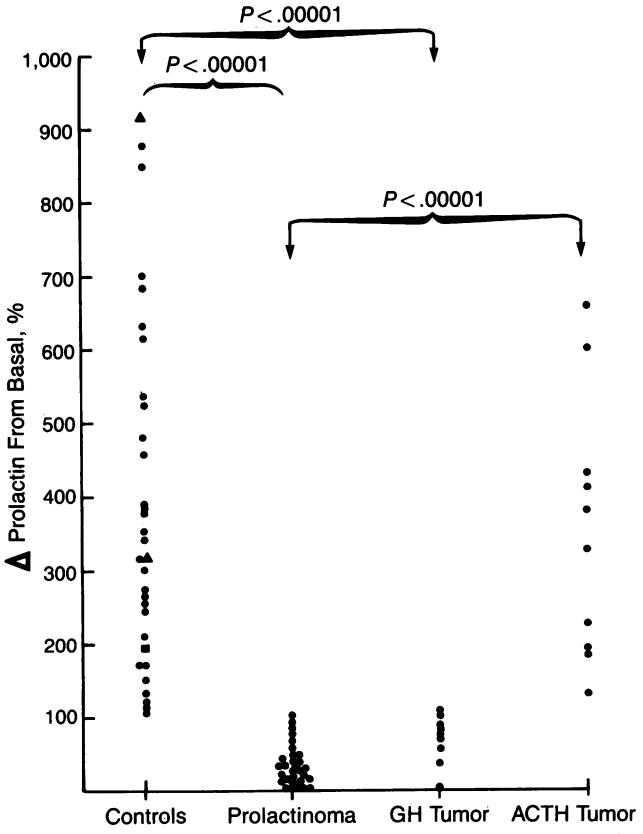

Figure 1.—The percent change in plasma prolactin levels in response to the administration of 500 μg of thyrotropin-releasing hormone preoperatively is shown. Basal prolactin concentrations in the prolactinoma group ranged from 22 to 1,560 ng per ml. Two patients in the control group with primary hypothyroidism are identified by triangles and have basal prolactin concentrations of 10 and 34 ng per ml, respectively. The basal prolactin concentration of the one patient with drug-induced hyperprolactinemia (identified by a square) was 95 ng per ml. Basal prolactin concentrations were less than 20 ng per ml in all patients with growth hormone (GH)- and adrenocorticotropin (ACTH)-secreting tumors and in the remaining control patients.

Individual basal and peak plasma growth hormone concentrations after TRH stimulation in the four groups are shown in Figure 3. A growth hormone response is defined arbitrarily as a level rising 100% or more above basal and a 5-ng-per-ml rise because spontaneous fluctuations could account for large percentage changes if basal values are low. Significant growth hormone responses to TRH stimulation in each group were as follows: control group 28%, prolactinoma group 20%, acromegalic group 25% and group with ACTH-secreting tumors 50%.

Postoperative Response

Not all patients were cured (Figure 4). The criteria for cure in patients with prolactinomas included normal prolactin

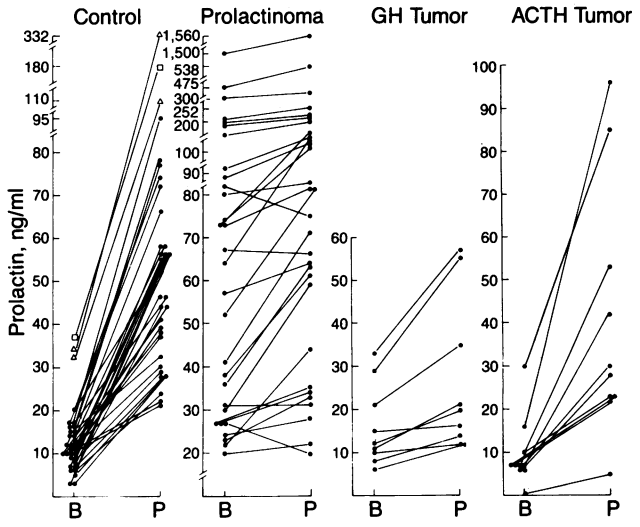

Figure 2.—The graphs show peak plasma prolactin responses (ng per ml) to thyrotropin-releasing hormone stimulation. The two patients in the control group with primary hypothyroidism are identified by triangles. The one patient with drug-induced hyperprolactinemia is identified by a square. ACTH = adrenocorticotropin, B = basal, GH = growth hormone, P = peak

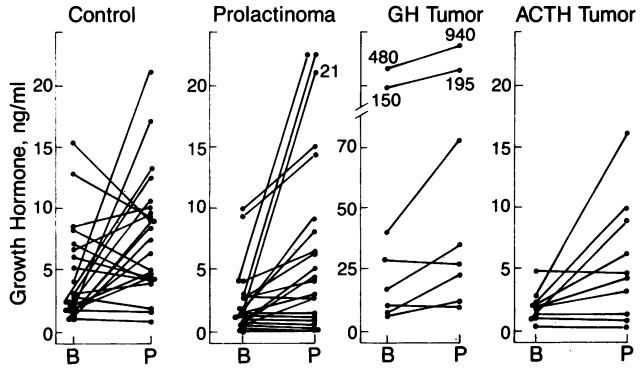

Figure 3.—Plasma growth hormone responses to the administration of 500 μg of thyrotropin-releasing hormone in a preoperative study are given. Absolute values are shown and suggest significant responses in all four groups. ACTH = adrenocorticotropin, B = basal, GH = growth hormone, P = peak

levels on at least three separate determinations and no evidence of an anterior pituitary deficiency. Patients not cured of prolactinoma included those in whom the surgeon believed not all the tumor was removed and patients who had persistent hyperprolactinemia. None of the noncured patients were thought to have hyperprolactinemia on the basis of isolation of the anterior pituitary from the hypothalamus. Prolactin responses to TRH in patients with prolactinoma and those with acromegaly were similar to those of controls in cured patients. Those not cured were persistently unresponsive. Patients with ACTH-secreting tumors were unchanged postoperatively whether cured or not. Not all patients returned for follow-up studies.

Discussion

Abnormal prolactin responses to TRH have been observed in most patients with prolactinomas.* Klijn and co-workers have suggested that this may be related to a tumor in the hypothalamic area because 7 of 11 patients they studied with suprasellar tumors that were not prolactinomas had blunted responses.[20] Our data suggest that other mechanism(s) for blunted responses may exist in growth hormone- and prolactin-secreting tumors.

It has been suggested that patients with prolactinomas may have a benign course.[21-23] Such studies that suggest spontaneous regression or stable growth characteristics, however, lack adequate proof that these patients actually have tumors. A prolactinoma may or may not be visible by high-resolution CT scan of the sella.[24-28] A reliable nonoperative means of identifying tumors would avoid an unnecessary operation and the undue worry if a tumor was not present and improve our knowledge of the natural history of this tumor. Our results suggest that prolactinoma patients do not respond to TRH stimulation with a change in plasma prolactin concentrations. Most series reporting false-positive responses do not have surgical and pathologic verification of prolactin-secreting tumors, and those that do have histologic proof tend to implicate TRH hyporesponsiveness.[7-19] Chlorpromazine stimulation tests have also been used to separate patients with prolactinomas from those with functional hyperprolactinemia. Boyd and associates found blunted prolactin responses to chlorpromazine stimulation in 4 of 6 prolactinoma patients and in 4 of 12 other patients with galactorrhea without evidence of adenoma.[15] Kleinberg and colleagues found blunted rises of serum prolactin levels after chlorpromazine stimulation in all nine patients with verified prolactinoma and in 19 of 36 patients with other forms of galactorrhea.[29] Zárate and coworkers showed normal responses to chlorpromazine in 8 of 16 patients with galactorrhea and amenorrhea, including 2 of 5 with pituitary tumors.[30] Our studies with TRH would suggest a lower incidence of false-positive responses compared with those with chlorpromazine.

*References 7-13 (p 225), 14-19 (p 131).

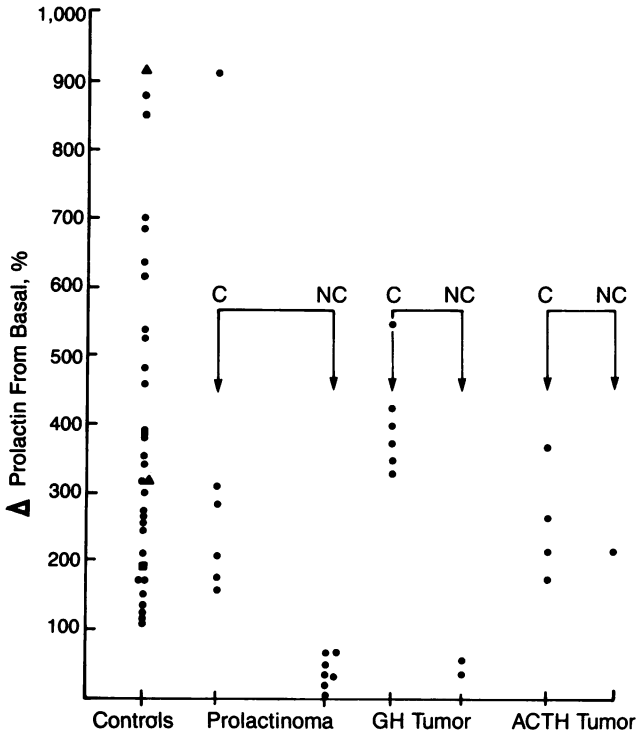

Figure 4.—Plasma responses to thyrotropin-releasing hormone stimulation reverted to normal in cured patients with prolactinomas and those with acromegaly. The responses in noncured patients in both groups were unchanged. ACTH = adrenocorticotropin, C = cured, GH = growth hormone, NC = not cured

Why patients with prolactinomas respond poorly to TRH stimulation is an unanswered question. Patients with hyperprolactinemia of a clearly secondary cause such as drug-induced or associated with hypothyroidism usually respond to TRH administration.[15,29,31] Other patients identified as functional may or may not respond.[7,11,12] Because this functional group has not had surgical exploration, we cannot be sure whether or not failure to respond may represent the presence of a tumor. Our series includes two patients with hyperprolactinemia due to hypothyroidism and one due to drug-related causes. All these responded vigorously to TRH stimulation. Our series of prolactinoma patients is important because all were clearly verified by a surgical procedure.

The finding of a persistent blunted response postoperatively in only the patients with prolactinoma and acromegalic patients not cured by surgical therapy suggests that the blunted response is not of hypothalamic origin or a generalized abnormality of lactotropes. It does suggest that a complete cure is possible by surgical treatment and that a return of prolactin responsiveness to TRH stimulation may be a marker for a surgical cure.

The diminished prolactin response to TRH administration in patients with prolactinoma and acromegalic patients is not explained at present. The absence of stored prolactin in tumor could be an explanation. We did not have immunocytochemistry staining to verify the presence or absence of prolactin in tumor cells. Clear responses in the secondary causes, however, suggest that some hyperprolactinemic states are not associated with exhaustion of stored prolactin. Pathologic studies using immunocytochemistry have verified the presence of stored hormone in some, but not all, prolactinomas. We do not know of a study showing a correlation between the absence of storage and blunted or absent prolactin responses to TRH. Until such studies are forthcoming, we will continue to look for the presence of a prolactinoma when serum prolactin responses to TRH stimulation are low or absent.

Hyperprolactinemic patients with chronic renal failure also have poor plasma prolactin responses to TRH.[32-35] Normal responsiveness does not return with dialysis but does with transplantation,[36] suggesting an inhibition at the pituitary level by a humoral factor other than prolactin because other functional causes of excess prolactin secretion such as

drug-induced and primary hypothyroidism are not associated with inhibition.

The growth hormone responses to TRH observed in both control patients and those with a pituitary tumor without acromegaly were surprising. Although previous studies[35,37,38] of growth hormone responses to TRH in controls disagree with our findings, closer inspection of these reports (especially that of Irie and Tsushima[37]) suggests that growth hormone may be significantly released by TRH stimulation in control subjects. Our findings imply that growth hormone response to TRH is not an exclusive tumor marker for acromegaly as 28% of the control patients, 20% of the patients with prolactinomas and 50% of patients with ACTH-secreting tumors had significant increases in growth hormone levels. Therefore, we suggest that the current clinical practice of accepting growth hormone responses to TRH stimulation[37,39-42] as evidence for acromegaly may not be valid.

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